Aerosolized Calfactant in Infants With RDS: Surfactant Replacement 2.0?

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The burden of preterm birth remains substantial, with immature infants surviving at rates higher than ever before but with significant morbidities.[1] Bronchopulmonary dysplasia is a leading cause of mortality and long-term impairments.[2] Given the direct relationship between invasive mechanical ventilation and lung injury, the search continues for strategies that help to successfully establish noninvasive support for management of respiratory distress syndrome. Alternative modes of surfactant administration in preterm infants spontaneously breathing on continuous positive airway pressure have been tested, with the goal of limiting exposure to mechanical ventilation.[3] However, there has not been clear-cut evidence that these approaches improve outcomes in high-risk infants so far.[4] Offered as a truly noninvasive approach, nebulization of surfactants avoids the harms of laryngoscopy.[3] Despite ongoing research, clinical data are scarce, and efficacy has yet to be assessed.[4–8]

In this issue of *Pediatrics*, Cummings et al[9] report rates of intubation and intratracheal surfactant therapy in 457 infants receiving noninvasive respiratory support for respiratory distress syndrome randomly assigned to either aerosolized calfactant or standard therapy (liquid surfactant per clinician judgment). The authors report that the bovine surfactant calfactant can be readily administered and that it significantly decreases the need for intubation and liquid surfactant administration within the first 4 days of age. Of note, respiratory support at day 3, 7, and 28 was not different among study groups.

This was a large randomized multicenter trial introducing a practical approach of nebulization that is compatible with continuous positive airway pressure, high-flow nasal cannula, and noninvasive ventilation. Importantly, application of surfactant aerosols was well tolerated by using a modified nebulizer with a pacifier interface. This result is promising and in accordance with previous pilot studies and a recent phase I clinical study documenting feasibility and safety of aerosolized surfactants in infants receiving noninvasive ventilation.[5–8]

Despite these promising results, the study design potentially introduced significant bias into the study. Notably, there were no criteria for surfactant therapy in the randomly assigned groups. The authors acknowledge this point, but it deserves further discussion. The study design did not dictate treatment thresholds in the liquid surfactant arm given the heterogeneity in clinical practice among the different study sites. Furthermore, there were not strict criteria defining treatment failure in the subjects randomly assigned to aerosolized surfactants, leaving the objective assessment of treatment effect unknown. Because this trial was unblinded, clinicians were aware that every infant randomly assigned to the nebulized surfactant arm received the intervention. It is possible that clinicians delayed intubation and

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endotracheal surfactant instillation in this group, being biased by aerosolization and the hypothesis of lower risk of air leak and lung injury.

Without a strict definition of failure, it is likely that there was great variation in the clinical decision to intervene with liquid surfactant treatment in the intervention arm. Importantly, clinical data at the time of treatment with liquid surfactants in both groups are missing. Objectively, such bias may have become manifest in higher airway pressures, higher oxygen supply, and delay in endotracheal surfactant instillation in the aerosolized group. Unfortunately, data on fraction of inspired oxygen, $Paco_2$, positive end-expiratory pressure, and mean airway pressure are not provided. Delay in endotracheal surfactant instillation was observed, occurring at 24 and 10 hours, respectively. Furthermore, this delay could be associated with unanticipated negative effects, such as increased oxygen exposure or delay in initiation of feeds. Importantly, these measures will have to be assessed in future trials.

In contrast to early surfactant trials, the burden of bronchopulmonary dysplasia has shifted to less mature infants. Today, it primarily affects infants born at <28 weeks' gestational age.[1] Despite the promising results presented here, only a minority of neonates enrolled represent this cohort. With gestational ages of 23 to 41 (median 33) weeks and birth weights of 595 to 4802 g (median 1960 g), most infants were more mature. The high risk of invasive mechanical ventilation–induced lung injury in tiny infants clearly contrasts with a rather low risk of laryngoscopy-associated complications in moderate preterm neonates. Although study infants at 33 weeks' average gestational age stood little risk of long-term complications associated with exposure to mechanical ventilation, we can hope that these results can be replicated in larger studies enrolling infants at the most vulnerable gestational ages (<28 weeks).

Nebulization of surfactants remains an attractive route because it avoids endotracheal manipulation, with the potential of reducing exposure to mechanical ventilation and, ultimately, decreasing the risk of lung injury. Although this study is promising and reveals safety and feasibility, a trial targeted at a less mature population is necessary before adopting this approach for preterm infants at highest risk of lung injury.

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